Image AF/1646

Attorney Docket No.: N12-023 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Sklar et al.

Serial No.: 09/370,358 Group Art Unit:1646

Filed: August 9, 1999 Examiner: Brannock, M.

For: DISPLAY OF RECEPTORS AND ANALYSIS OF BINDING INTERACTIONS AND DRUG LIBRARIES

TRANSMITTAL OF REPLY BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer dated January 8, 2004, Appellants herewith enclose a Reply Brief. An executed revocation and power of attorney form is also enclosed. Please refer to matter no. **N12-023** when reporting correspondence associated with this matter.

Respectfully submitted,

Dated: March 8, 2004

Henry D. Coleman
Reg. No. 32,559
Coleman Sudol Sapone, P.C.
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
(203) 366-3560

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I hereby certify that this correspondence is being sent by first class mail in an envelope addressed to the Commissioner of Patents, Mail Stop Non-Fee Amendment, P.O. Box 1450, Alexandria, VA 22313-1450 on March 8, 2004.

Henry D. Coleman, Reg. No. 32,559

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In re Application of: Sklar et al.

Serial No.: 09/370,358 Group Art Unit: 1646

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REPLY BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer dated January 8, 2004, Appellants herewith submit the instant Reply Brief. Appellants will address below each of the points made in the Examiner's Answer. However, before doing so, Appellants will provide a brief summary of the relevant case law.

I. Case Law

As noted in Examiner's reply, *In re Kotzab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000), stated that the test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. However, Appellants wish to point out that the Court in *Kotzab* actually had determined that the claims at issue were not obvious over a combination of references. Furthermore, the court in *Kotzab* stated

> Most if not all inventions arise from a combination of old elements (citations omitted). However, identification in the

> prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention..Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *Id*

A later decision, *Ecolochem Inc. v. Southern California Edison Company,* 227 F.3d 1361, 56 USPQ2d 1065(Fed. Cir. 2000) also addressed the patentability of a claim rejected over a combination of references. In reversing the Board's decision, the Court in *Ecolochem* stated

> "[t]he suggestion to combine may be found in explicit or implicit teachings within the references themselves, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved (citation omitted). However, there still must be evidence that "a skilled artisan, confronted with the same problems as the inventor and with knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." (citation omitted). *Id at* 1075.

Ecolochem further addressed the issue of the improper use of hindsight. Specifically, although the suggestion to combine references may flow from the nature of the problem, defining the problem in terms of its solution is an indication of the use of hindsight in the selection of the prior art relevant to obviousness. *Id* at 1073. It is well established case law that hindsight reconstruction cannot be used "to pick and choose among isolated disclosures in the prior art to deprecate the prior art". *In re Fine*, 837 F.1071, 5 USPQ2d 1780 (Fed. Cir. 1988).

II. The Rejections

A. The rejection of claims 1, 6, 9-13, 15-17, 48, 50, 51 and 53-57 over U.S. Patent No. 5,583,010 (Baumbach) in view of U.S. Patent No. 5,639,603 (Dower)

The following grounds for this rejection were given on pages 3-5 of the Examiner's Answer:

> U.S. Patent No: 5583010 disclose methods for non-cellular display (e.g. purified recombinant receptor, col 19, L65) of a 7TM receptor (Growth hormone releasing hormone receptor GHRH-R) comprising incorporating an attachment scheme to the receptor (col 20, L1-3), solubilizing the receptor by lysing cell membranes containing the receptor (e.g. col 10, L24-29), presenting the receptor with [sic] in conjunction with a solid support (col 19 L65-col 20 L12), presenting one ligand to bind to the receptor, wherein said ligand is known to bind to the receptor (e.g. GHRH), and combining receptor and ligand to accomplish binding (col 19 L65-col 20 L12). Also, U.S. Patent No: 5583010 state[s] that "these assays can be linked to a reporter such as an antibody, biological chemical..., which will express a radioactive, chemical, calorimetric or luminescent signal" see col 20 L4-7; thus one of ordinary skill in the art would understand from this teaching, and particularly from the term "luminescent signal", that it is meant the receptor ligand pairs can be sorted by fluorescence.
>
> The claims also stipulate that the method of sorting be flow cytometry and that the solid support be bead substrates appropriate for flow cytometry. Additionally claims 54-57 requires that the tag be an epitope tag, e.g. either an N or C-terminal, or internal epitope. One of ordinary skill in the art appreciates that at col 20, first paragraph, U.S. Patent No: 5583010 refers to such attachment means in the statement "Solid phase assays can involve receptor attached to a solid support either chemically or immunologically..."
>
> Although U.S. Patent No: 5583010 appears to be silent with regard to flow cytometry, flow cytometry is a well known method of sorting fluorescently labeled receptor-ligand pairs. U.S. Patent No: 5639603 teaches the general applicability of flow cytometry to the sorting of isolated solubilized receptors and their bound ligands, wherein the solid supports are beads appropriate for flow cytometry and for library screening (see col 31, L40-54). Further, Patent No: 5639603 teaches that the receptor (e.g. col 31, L58) or the ligand (col 36, L35-38) be labeled with a fluorescently labeled marker.
>
> Therefore it would have been obvious to one of ordinary skill in the art, at the time the invention was made, and with

> reasonable expectation of success to use beads as the solid support and to separate the receptor-ligand pairs by flow cytometry as taught by U.S. Patent No: 5639603, when practicing the assay of soluble receptors attached to solid supports as taught by U.S. Patent No: 5583010. The motivation to do so was provided by U.S. Patent No: 5639603 wherein it is taught that "by adopting cell sized solid supports or beads, one can use flow cytometry for high sensitivity receptor binding analysis and facile bead manipulation" (see col 31, L47-54).

It is further stated on page 8 of the Examiner's answer:

> Appellant argues that no grounds have been provided as to why a person of ordinary skill in the art would be motivated to combine Dower and Baumbach. This argument has been fully considered but not deemed persuasive. The motivation to do so was provided by Dower wherein it is taught that "by adopting cell sized solid supports or beads, one can use flow cytometry for high sensitivity receptor binding analysis and facile bead manipulation" (see col 31, L47-54). Baumbach teach the desirability to perform ligand binding assays using a bound receptor and ligand, e.g. col 19 L65-col 20 L12. Dower teach a refined method for performing such assays, e.g. flow cytometry, therefore it would be obvious for one of ordinary skill in the art practicing the general teachings of Baumbach regarding assay systems to turn to the more refined method of Dower.
>
> Appellant argues that Baumbach and Dower fail to teach or suggest analyzing with a flow cytometer in real time as recited in claim 1. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art appreciates that, even with the wash step (exclusion of which is not a positive claim limitation), Dower teaches analyzing with flow cytometry in real time, i.e. the disassociation of the ligand and the receptor is happening as they are being analyzed in the flow cytometer. Appellant has done essentially the same thing.
>
> Appellant argues that the methodology employed by Dower differs in several respects from claim 1; namely that Dower solubilizes and binds a ligand library to a bead whereas claim 1 requires that the receptor be attached to a bead via a tether. This argument has been fully considered but not deemed persuasive. First, Appellant is reminded that the rejection is under 35 USC 103, therefore no single prior art

> reference need teach each and every limitation; otherwise the rejection would be under 35 USC 102. Secondly, Dower reviews many particular ways of performing the assay e.g. with the ligand immobilized, as referred to by Appellant, or with the receptor immobilized.... All of these configuration[s] would be obvious to one of ordinary skill in the art depending on the particular application required.

In response, Appellants assert that both Baumbach and Dower teach a number of methods for assaying ligand binding to receptors. Specifically, Baumbach teaches assaying the binding of ligand[s] to receptor[s] both in solution and when the receptor[s] are attached to a solid support. However, the disclosure in Baumbach regarding the performance of ligand binding assays using a support-bound receptor and ligand is rather limited. Specifically, the **only** disclosure in Baumbach regarding the performance of ligand binding assays using a bound receptor is the paragraph bridging columns 19 and 20:

> Screens use the purified or recombinant receptor in solid or liquid phase or in a host cell. Expression in the screen is measured by ligand binding, second messenger function, product secretion, or by other means. Solid phase assays can involve receptor attached to a solid support either chemically or immunologically in conjunction with or without transduction proteins These assays can be linked to a reporter such as an antibody, biological chemical (e.g., biotin), or binding protein or enzyme, which will express a radioactive, chemical, calorimetric or luminescent signal. Screens involving host cells can employ bacterial or higher cells ...Ideal mammalian host cells include pituitary tumor cell lines which secrete GHRH, and cell lines secreting other products in response to stimulation of the transfected GHRH-R.

Clearly, this disclosure in Baumbach is very limited. There is certainly no disclosure regarding the wisdom of solubilizing receptors before attaching to the support. Furthermore, Baumbach teaches attaching the receptor to the support via chemical or immunological means and optionally adding reporter molecules. However, in the method of the present invention, the tether can indeed be a reporter molecule such as biotin. The teaching of solubilizing receptors is as noted in the Examiner's response in column 10,

lines 24-29. There is also a teaching in column 28, lines 15-31 regarding solubilization. However, these disclosures all are in relation to assays conducted in solution and concern the solubilization of **receptor-GHRH complexes, not the receptor** alone. The solubilization of receptor-GHRH complexes is certainly different from just solubilizing the receptor itself. One of ordinary skill in the art may actually conclude that it may not be wise to solubilize the receptor before attaching to a solid support.

Most of the Baumbach disclosure concerning assaying receptor-ligand binding is mainly concerned with assaying in solution. None of the figures show results where the receptor is bound to a solid support. The working examples (see, in particular, columns 28-30) disclose assay methods in solution. Thus, one of ordinary skill in the art seeing how much attention is devoted to assaying ligand-receptor binding in solution would be more inclined to perform such assays in solution. Therefore, it is doubtful whether one of ordinary skill in the art would be motivated to combine the disclosures of Baumbach with Dower.

The Examiner is certainly correct in asserting in his answer that Dower indeed reviews many particular ways of performing the assay e.g., with the ligand immobilized, as referred to by Appellant, or with the receptor immobilized. For example, in column 4, lines 1-14:

> In one important embodiment, the invention provides a method for performing peptide and oligonucleotide synthesis on microscopic beads through an alternating and compatible synthetic procedure. The large oligonucleotide-encoded synthetic peptide library produced by this combinatorial synthesis is composed of many beads, each of which contains many copies of a single peptide (with a defined sequence) and a single-stranded DNA tag whose sequence artificially and unambiguously codes for the structure of the associated peptide. The library can be efficiently interrogated for interaction with fluorescently labeled biological receptors by flow cytometry, and individual beads selected by exploiting the ability of FACS instrumentation to sort single beads. .....

The sole reference to using immobilized receptors in Dower is actually at column 36, lines 28-43:

> Soluble tagged molecules can also be screened using an immobilized receptor. After contacting the tagged molecules with the immobilized receptor and washing away nonspecifically bound molecules, bound tagged molecules are released from the receptor by any of a wide variety of methods. The tags are optionally amplified and then examined and decoded to identify the structure of the molecules that bind specifically to the receptor. A tagged oligomer in solution can be assayed using a receptor immobilized by attachment to a bead, for example, by a competition assay with a fluorescently labeled ligand. One may recover the beads bearing immobilized receptors and sort the beads using FACS to identify positives (diminished fluorescence caused by the library molecule competing with the labeled ligand). The associated identifier tag is then be[sic] amplified and decoded.

No direction is provided in Dower regarding what option would actually be preferable, immobilized receptors or immobilized ligands. One of ordinary skill in the art given the disclosures of Baumbach and Dower, may be inclined to combine the disclosure of Baumbach with respect to use of assaying ligand-receptor interactions in solution with the disclosure of Dower regarding the use of ligand immobilized to beads as opposed to combining the disclosures of Baumbach and Dower with respect to immobilized receptors. At best, the combination of Baumbach and Dower would be obvious to try. It is well established case law that "obvious to try" is not the correct standard. *Ecolochem, Inc. v. Southern California Edison Company,* 227 F.3d 1361, 56 USPQ2d 1065(Fed. Cir. 2000); *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). Furthermore, as in *Ecolochem*, it appears that the disclosure of the instant application was used as a blueprint for Baumbach as the main structural diagram . The disclosure of Dower was used to fill in the element of flow cytometry. This is clearly hindsight, which as discussed above, is not permissible.

Appellants further point out that *contra* to assertions made in the Examiner's answer, neither Baumbach nor Dower discloses solubilizing the receptor itself before immobilizing to a support. Furthermore, Dower discloses using FACS either **after** tagged molecules are released from the receptor or recovering beads bearing immobilized

receptors and sorting the beads using FACS to identify positives. No direction is provided regarding what option would actually be preferable.

In summary, given the paucity of teaching in Baumbach regarding immobilized receptors, the lack of teaching of solubilizing receptors in either Baumbach or Dower, the teachings of both immobilized receptors and immobilized ligands in Dower and lack of direction regarding what would be preferable, and the teaching of the use of FACS both after a wash step and in a competition assay, it would not be obvious to combine the disclosures of Baumbach with Dower. Therefore, the rejection should be withdrawn.

B. The Rejection of Claims 2-5 and 8 over U.S. Patent No. 5,583,010 (Baumbach) in view of U.S. Patent No. 5,639,603 (Dower), and further in view of Robeva, 1996, Drug Devel. Res. 39:243-252

The following grounds for this rejection were given on pages 35-36 of the Examiner's Answer:

> Claims 2, 3-5 and 8 stipulate that the tether or attachment means must be a C-histidine or an N-histidine tag and that the bead be a Ni-silica bead and that the step of solubilizing the receptor comprise lysing the cell membranes. The use of histidine tags in the receptor art is old. Further, it is well known that Ni-silica beads are used with histidine tags. Robeva et al. disclose a method of displaying a 7TM receptor (Adenosine receptors) comprising incorporating an attachment scheme (e.g. hexahistidine tag) into the Adenosine receptor (GPCR construct), solubilizing the receptor by lysing membranes comprising the receptor (page 245), presenting the receptor on a solid support (e.g. NiNTA agarose, page 245), wherein said method further comprises the step of combining the receptor and a ligand to accomplish binding (see page 244, col 2).
>
> Additionally, whether to use [the] tag at the N or C-terminal is an obvious matter of routine optimization of operating parameters. Further, Robeva teach that the step of incorporating an attachment scheme comprises incorporating the tag (coding sequence) into an oligonucleotide: see page 244, MATERIALS AND METHODS, wherein the method of subcloning the Adenosine receptor is referenced in Robeva et al., 1996, Biochem. Pharm. 51:454-555, wherein it is indicated that

> the tags are incorporated using a 30 base pair oligonucleotide, see Robeva et al., 1996, Biochem. Pharm, page 554.
>
> Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to, with reasonable expectation of success to use histidine tags taught by Robeva, as the attachment means for the assay disclosed by U.S. Patent No: 5583010 and modified according to the teachings of U.S. Patent No: 5639603, as discussed above. The motivation to do so was provided by Robeva AS et al., Drug Development Research wherein it is stated that their method should be useful for other proteins and for a variety of methods including reconstitution assays (see page 554), reconstitution assays being required for solubilization of the receptor, as per the instant invention.

Appellants respectfully disagree with the position set forth in the Examiner's answer. It would not have been obvious to use histidine tags taught by Robeva as attachment means for the assay disclosed by Baumbach and Dower. This is because of other teachings of Robeva. In Robeva, receptors are purified by affinity chromatography. Assays for ligand-receptor binding are actually performed in solution. Specifically, hexahistidine/FLAG-tagged receptors are solubilized, then immobilized and eluted from an Anti-FLAG affinity column and immobilized and eluted from nickel-nitrilotriacetic acid affinity column. As described on page 244, (column 2) of Robeva, radioligand binding assays were conducted in solution. Thus one of ordinary skill in the art would not have a reasonable expectation of success that an immobilized hexahistidine tagged receptor could actually be used in receptor-ligand assays, particularly, the receptor – ligand assays of the present invention. At best, Robeva merely teaches that 7-transmembrane receptors may be tagged with a histidine tag. No indication is given that a solubilized histidine-tagged 7-transmembrane receptor could actually be attached to a solid support via a tether and assayed for binding to various ligands **while** attached to the support.

Additionally for the reasons described above, it would not have been obvious to combine the disclosures of Baumbach and Dower since there is a paucity of teaching in

Baumbach regarding immobilized receptors, there are teachings of both immobilized receptors and immobilized ligands in Dower and lack of direction regarding what would be preferable, and the teaching of the use of FACS both after a wash step and in a competition assay.

In grouping Robeva, Baumbach and Dowever together, the Examiner appears to be extracting out (essentially, "cherry-picking") discrete elements from each of them. This includes from Baumbach, the teaching of receptor-ligand assays, where the receptor is immobilized to a solid support, from Dower, the teaching of using flow cytometry and from Robeva, the teaching of tagging the transmembrane receptor with hexahistidine. However, as noted above, the other teachings in each of these references were ignored. This combination again is another example of the improper use of hindsight. In yet another Federal Circuit decision, *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992) the court states that

> It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious ....This court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention'

In summary, since there would not have been a motivation to combine the cited references, the rejection involves the impermissible use of hindsight and at best the combination is an "obvious to try" situation, Appellants assert that the rejected claims are not obvious. Therefore, Appellants request that rejection be withdrawn.

III. Conclusion

In conclusion, Appellants respectfully assert that based on the arguments set forth above and in previous documents submitted, the cited prior art does not provide any reason for combining the claimed ingredients. Therefore, the PTO's rejection of the

present claims under 35 U.S.C. 103 are in error. Reversal of the rejection by the Board is therefore respectfully solicited.

Respectfully submitted,

Dated: March 6, 2004

Henry D. Coleman

Reg. No. 32,559
714 Colorado Avenue
Bridgeport, Connecticut 06605-1601
(203) 366-3560

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Henry D. Coleman, Reg. No. 32,559